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EVALUATION OF THE QUALITY OF GUIDELINES FOR ESSENTIAL TREMOR TREATMENT WITH THE AGREE II INSTRUMENT

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RESUMO

O tremor essencial é uma perturbação neurológica reconhecida como uma das mais comuns doenças do movimento e que pode ser incapacitante e repercutir-se negativamente na qualidade de vida dos doentes. A abordagem do tremor essencial deve ser ajustada ao grau de incapacidade do doente e o actual tratamento é primariamente farmacológico, enquanto procedimentos cirúrgicos são reservados para casos mais graves e refractários. Ainda assim, muitos doentes são mal controlados e revisões da literatura apontam uma escassez de estudos direccionados à terapêutica no tremor essencial, o que resulta num limitado número de normas de orientação clínica (NOC's) para o tratamento desta perturbação. Este artigo tem como objectivo realizar uma pesquisa sistemática da literatura para identificar todas as NOC's disponíveis dirigidas ao tratamento do tremor essencial, quer internacionais quer regionais, para avaliar a sua qualidade metodológica usando o instrumento *Appraisal of Guidelines for Research and Evaluation II* (AGREE II). Também se pretende extrair as principais recomendações sobre este tópico e comparar a sua consistência. Este artigo visa beneficiar o futuro desenvolvimento de NOC's sobre tratamento do tremor essencial que tenham superior qualidade metodológica.

ABSTRACT

Essential tremor (ET) is a neurological disorder widely recognized as one of the most common movement disorders and can sometimes be disabling, negatively affecting patient's life quality. ET approach should be adjusted to patient's degree of disability and current management is primarily pharmacological, while surgical procedures are usually reserved for more severe and refractory cases. Nonetheless, many patients are poorly controlled and reviews of the literature have emphasized the paucity of studies targeted at analyzing treatment options for ET, which in turn results in a limited number of clinical practice guidelines for the treatment of this disorder. The purpose of this study is to systematically identify all available international and regional guidelines addressing ET treatment and evaluate their methodological quality using the AGREE II instrument. Another objective is to extract key recommendations on this subject and compare their consistency. This article aims to benefit the future development of guidelines concerning the treatment of ET with superior methodological quality.

Evaluation of the Quality of Guidelines for Essential Tremor Treatment with the AGREE II instrument

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BACKGROUND

Essential tremor is a neurodegenerative disorder that is widely recognized as one of the most common adult-onset movement disorders. [1-5] A meta-analysis from 2010 used population-based studies (n = 28) to estimate that the age independent pooled prevalence of ET was 0.9% and established an increasing prevalence with age (prevalence being 4.6% for individuals $\geq$ 65 years old).[1,6]

Classically, it is clinically characterized by bilateral, largely symmetrical, postural (which manifests during voluntary maintenance of a position against gravity) and/or kinetic (revealed with voluntary movement) tremor involving the upper limbs (in at least 95% of patients) and less commonly the head, face/jaw, voice, tongue, trunk, and lower limbs, in the absence of other neurologic signs.[7-9]

However, ET is a heterogeneous disorder and there is little agreement regarding both clinical definition and diagnostic criteria.[10,1] Moreover, besides the described action tremor, patients may manifest intention tremor [12], rest tremor,[13] and ataxia[14]. In addition to these motor signs, it has been suggested an increased risk for neuropsychiatric manifestations such as cognitive impairment, dementia, [15,16] depression and personality disorders. [17]

The underlying pathophysiological mechanisms are still not well elucidated. Nonetheless, the fundamental abnormality in ET is an abnormal motor unit entrainment at frequencies of 4–12 Hz.[18] Substantial clinical, neuroimaging and neurophysiological data support the hypothesis that this motor unit entrainment emerges from neuronal oscillation in the cortico-bulbo-cerebello-thalamo-cortical loop network but the cause for oscillation in ET is unknown.[19-23]

Genetic susceptibility has a long been identified as having significant role in essential tremor. [24] There is a positive family history in at least 50-70% of cases and transmission is thought to be autosomal dominant, with high genetic penetrance by age of 65 years.[25,26]

Although presumably thought to not affect life expectancy, the diagnostic term “benign essential tremor” has been appropriately decommissioned with the growing appreciation that ET often produces substantial social or physical disability.[27, 28] Affected patients represent a heterogeneous population and severe cases could be very disabling.[29] ET is usually progressive and patients may experience difficulties performing basic daily

activities, thereby impairing quality of life.[27] Furthermore, 90% of patients who seek medical care report disability and severely affected end-stage patients are unable to feed or dress themselves. 15–25% of patients are forced to retire prematurely, and 60% choose not to apply for a job or promotion because of uncontrollable shaking.[30]

ET approach should be tailored to patient's degree of disability. Current management is primarily pharmacological, aimed to improve function and limit embarrassment caused by ET, while surgical procedures are reserved for more disabling cases. [31] Despite the high prevalence of this disorder and many patients poorly controlled, there is a lack of published recommendations focused on establishing and regulating its treatment. Furthermore, systematic reviews of the literature have emphasized a paucity of studies targeted at analyzing additional and current pharmacological and surgical treatments for ET. An explanation relies on scarce interest of the pharmaceutical industry in developing new drugs and to perform expensive clinical trials with adequate methodology on old drugs. [32]

In order to assist physicians and patient decisions on specific circumstances, clinical practice guidelines (CPG) were developed as tools that convey scientific evidence into clinical practice with the ultimate goal of improving healthcare quality. [33] To ensure that CPGs can meet this goal, internationally recognized, valid, reliable and feasible standards should be developed to assess the quality of guidelines and to promote their rigorous development.[34,35]

Accordingly, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument is a validated tool that has been endorsed by leading producers, raters and compilers of international CPGs to provide a framework to assess the methods used by the guideline developers.[36] To our knowledge, there are no published assessments of guideline quality for ET treatment.

Our purpose is to identify international or regional guidelines addressing ET treatment and evaluate their methodological quality using the AGREE II instrument. A secondary objective is to extract the recommendations stated on the guidelines and compare their consistency. This article is targeted to neurologists or other physicians who deal with ET on a regular basis in their clinical practice. Additionally, it may be valuable to former or future guideline developers concerning the treatment of Essential Tremor, in order to improve methodological strategies.

METHODS

The methods used in this appraisal were structured in phases: searching for guidelines, applying selection criteria, evaluating guideline quality, extracting recommendations and grouping them into standardized categories for comparison across guidelines.

Search strategy

A systematic literature search was conducted to identify evidence-based clinical practice guidelines for ET treatment. The National Guideline Clearinghouse, PubMed, MEDLINE, Cochrane Database of Systematic Reviews, National Institute for Health and Care Excellence (NICE), Guidelines International Network (G-I-N) and Web of Science databases were searched. Homepages of international medical societies and institutions were also screened for current CPG publications.

In addition, neurologists with expertize on tremor from different countries amongst members of the International Parkinson and Movement Disorder Society (MDS-PAS) were consulted and questioned whether they were aware existing national or regional CPG on ET treatment. Starting from 30th March 2015, a total of 570 physicians were contacted with individually addressed e-mails from which 83 replies were attained.

Eligibility criteria

We considered published documents with systematically developed recommendations on treatment of essential tremor.[37]

Precise pre-defined selection criteria were applied to identify articles eligible for quality appraisal (*Appendix 1*). To upturn the number of guidelines attained no exclusion criteria based on language or publication date were defined. Research articles, guidelines for use in clinical trials and systematic reviews were excluded. No ethics approval was needed considering the systematic critical appraisal nature of this article.

Methodological quality appraisal of the included guidelines

The guidelines were evaluated using the AGREE II instrument.[38] This refined tool provides criteria to appraise the quality of clinical practice guidelines [38] and consists of 23 key items organized within 6 domains followed by an overall quality assessment of every guideline: 1) *scope and purpose*: overall objectives of the guideline, target population and health question; 2) *stakeholder involvement*: guideline development

process and preferences of target population; 3) *rigor of development*: the process to assemble and resume evidence, the recommendation development process and its updating tools; 4) *clarity of presentation*: language, structure and format of CPG; 5) *applicability*: looking at barriers and facilitation to implementation, strategies to improve uptake; 6) *editorial independence*: pointing biases resulting from competing interests.[39] Each item, including the global rating item, is rated on a scale ranging from *strongly disagree* (1) to *strongly agree* (7) and the assigned score is based on the item's completeness and quality, increasing as more criteria and considerations detailed on the AGREE II manual were met. If the guideline had no relevant information on a certain item, it was rated as 1.

At the end of each appraisal, the evaluator has to make a judgment as to the overall quality of the guideline by again giving a score from 1 to 7 and defining if the guideline is recommended for use, recommended for use but with modifications, or not recommended for practice.

The guidelines were independently rated by 4 evaluators (RS, GD, CS and CS), after studying the AGREE II user manual[39] and using the online training tool found on the Resource Centre of the AGREE website[40] When necessary, appraisers had support from senior assistants with experience applying the AGREE II instrument. An inter-appraiser scores concordance on each domain was addressed and the attained standard deviation amongst evaluators for each item was less than 2,00 with a low discrepancy.

Standardized domain scores are calculated by summing up all scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain.[39]

Although the domain scores are useful for comparing guidelines and will inform whether a guideline should be recommended for use, the AGREE Consortium does not set minimum scores to differentiate between high quality and poor quality guidelines. [39] These decisions should be guided by the context in which AGREE II is being used and in this paper we considered a domain score greater than 60% as *effectively addressed*.

Thus, a guideline was labelled as *recommended* if at least three out of the six domains, including rigour of development (domain 3), were *effectively addressed*. [41] Guidelines were *recommended with modifications* if four domains scored between 30 and 60%, or

two domains scored higher than 60%. If four domains scored less than 30%, the guideline was considered as *not recommended* for use in clinical practice.

Extraction of the guidelines' recommendations

In addition to appraising the methodological quality of CPGs, recommendations for treatment of Essential Tremor were identified for data extraction. This analysis was independently performed by two members from the development group (RS and GD). The existence of a grading system to stratify the level of evidence was sought out in each CPG and if present its' source was registered and scrutinized for further strength of recommendation correspondence.

A chart was created to summarize the key characteristics of the selected guidelines: guideline developers; year; language, funding, addressed disorders, focus of guideline, target population and users, and existence of a grading system to stratify the level of evidence. (*Table 1*)

Recommendations were only extracted if the level of evidence or the strength of recommendations were clearly described for each recommendation. If the authors only provide the level of evidence, the extraction would only be carried out if it was obvious to infer the degree of recommendation. Extracted recommendations were grouped considering the form of essential tremor (limb, head, voice) and further divided between pharmacological and surgical treatments.

RESULTS

Search results

The overall search and guideline selection process is illustrated in the following diagram.

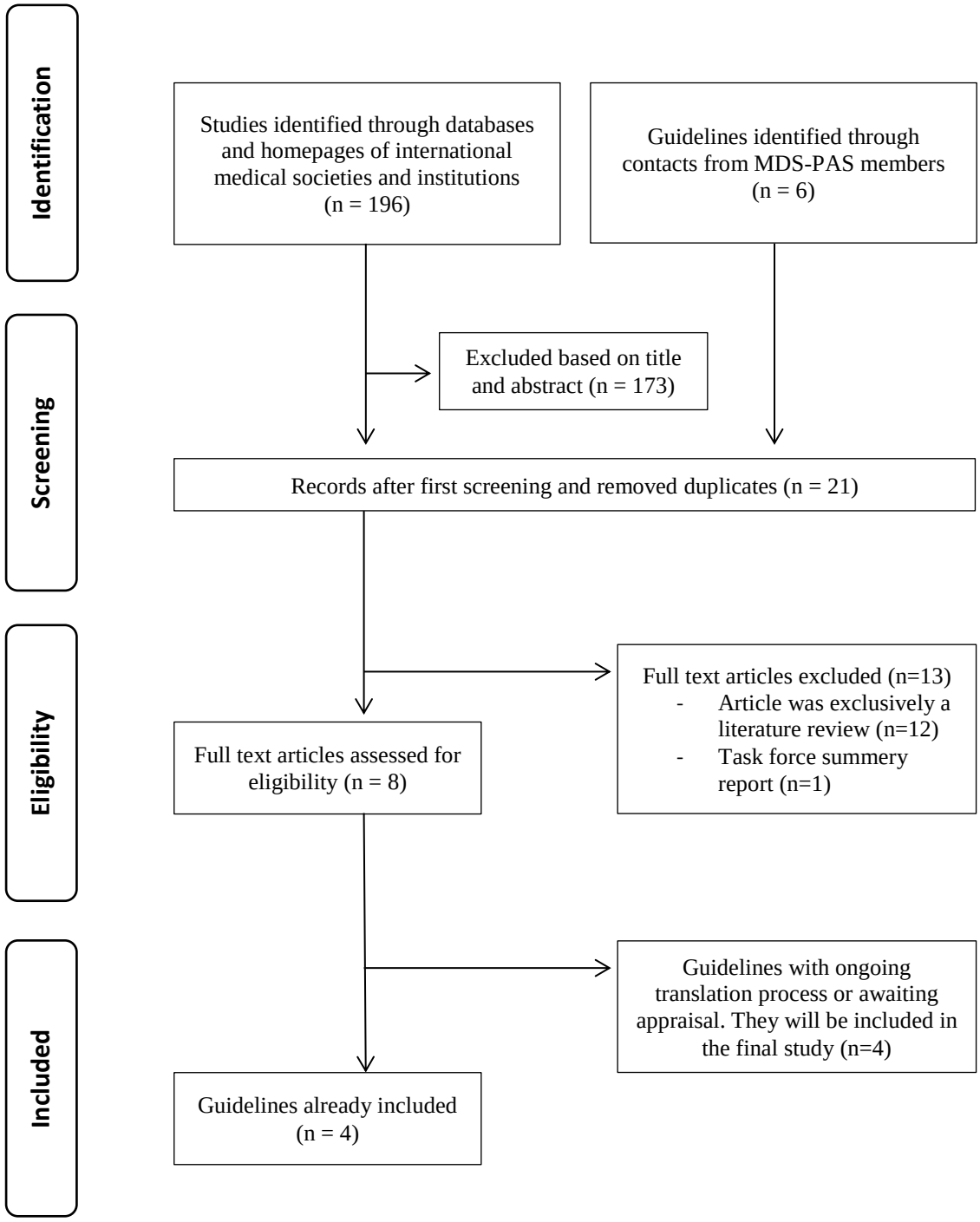

Figure 1. Searching and selecting guidelines flow diagram

Regarding MDS contacts via email most replies revealed inexistence of local recommendations or were only translations from the AAN guidelines. This consultation resulted in identification of CPG from Sweden, Germany and Japan, all of which were written in the respective native languages.

After screening, eight publications [42-49] were eligible for this critical appraisal.

***Table 1*:** Characteristics of selected guidelines

Developer	Year	Language	Funding	Addressed disorders	Focus of guideline	Target population	Target users	Grading system to stratify the level of evidence
AAN[42]	2005	English	NS	Essential Tremor	Practice parameter	Patients with ET	Physicians, neurologists	*American Academy of Neurology system*
AAN[43]	2011	English	Yes, by AAN	Essential Tremor	Update previous practice parameter	Patients with ET	Physicians, neurologists	*American Academy of Neurology system*
AIAN[44]	2011	English	NS	Essential Tremor	Management	Patients with ET	NS	*American Academy of Neurology system*
DISMOV-SIN[45]	2013	English	Yes, by DISMOV-SIN	Essential Tremor	Systematic review, treatment recommendations	Patients with ET	Physicians	*GRADE system*
SWEMODI[46]	2014	Swedish	NS	Drug induced tremor, Essential tremor, Orthostatic tremor, Dystonic tremor, Parkinson's disease Cerebellar tremor	Diagnosis Management	Patients with tremor	Healthcare professionals	NS
DGN[47]	2012	German						
JSNT[48]	2011	Japanese						
CAN[49]	2009	Chinese						

AAN: American Academy of Neurology; **AIAN**: Annals of Indian Academy of Neurology; **DISMOV-SIN:** Italian Movement Disorders Association; **DGN**: German Society of Neurology; **SWEMODIS:** Swedish Movement Disorders Society; **JSNT:** Japanese Society of Neurological Therapeutics. **CAN:** Chinese Association of Neurology; NS: not stated

Evaluation of guidelines

The methodological quality assessment for each domain is provided in *Table 2*. Scores ranged from 2,78%-92,59% across all the evaluated guidelines. Two guidelines[43,45] were considered as "*Recommended*" since more than three domains scored over 60%. One guideline[42] was considered "*Recommended with modifications*" while one [44] was "*Not Recommended*".

***Table 2*:** Domain scores of the CPGs assessed using the AGREE II instrument (scores >60% are highlighted in green)

	Domain 1. Scope and Purpose	**Domain 2.** Stakeholder Involvement	**Domain 3.** Rigor of Development	**Domain 4.** Clarity of Presentation	**Domain 5.** Applicability	**Domain 6.** Editorial Independence	***CPG Result***
AAN 2005	**72,22%**	53,70%	55,56%	**92,59%**	2,78%	25,00%	***Recommended with modifications***
AAN 2011	**66,67%**	57,41%	**61,11%**	**87,04%**	5,56%	**86,11%**	***Recommended***
AIAN 2011	24,07%	14,81%	13,19%	**75,93%**	5,56%	36,11%	***Not Recommended***
DISMOV-SIN 2013	**96,30%**	51,85%	**84,03%**	**92,59%**	5,56%	58,33%	***Recommended***
SWEMODIS 2014							
DGN 2012							
JSNT 2011							
CAN 2009							
Mean	64,82%	44,44%	53,47%	87,04%	4,87%	51,39%	
Standard deviation	30,05%	19,89%	29,55%	7,85%	1,39%	26,98%	

AAN: American Academy of Neurology; **AIAN**: Annals of Indian Academy of Neurology; **DISMOV-SIN:** Italian Movement Disorders Association; **DGN**: German Society of Neurology; **SWEMODIS:** Swedish Movement Disorders Society; **JSNT:** Japanese Society of Neurological Therapeutics. **CAN:** Chinese Association of Neurology; NS: not stated

Domain 1: Scope and Purpose. This domain had a mean score of 64,81% ± 30,05%. The guideline from the Italian Movement Disorders Association scored the highest at 96,3%. Lowest score (24,07%) was addressed by Annals of Indian Academy of Neurology guideline.

Domain 2: Stakeholder Involvement. All guidelines scored under 60% with a mean score of 44,44% ± 19,89%.

Domain 3: Rigor of Development. The mean score was 53,47% ± 29,55%. The guideline from the Italian Movement Disorders Association scored the highest at 84,03%. Lowest score (13,19%) was addressed by Annals of Indian Academy of Neurology guideline.

Domain 4: Clarity of Presentation. All guidelines scored above 60%, ranging from 75,93% to 92,56%. The mean score was 87,04 % ± 7,85%.

Domain 5: Applicability. All guidelines scored under 10% with a mean score of 4,87% ± 1,39%.

Domain 6: Editorial Independence. The mean score was 51,39% ± 26,98%. The guideline from 2011 by the American Academy of Neurology scored the highest at 86,11%. Lowest score (25%) was also addressed by the American Academy of Neurology on their guideline from 2005.

Clarity of Presentation (87,04% ± 7,85%.) was the highest rated domain and the one effectively addressed by all evaluated guidelines. Scope and purpose (64,81% ± 30,05%) was effectively addressed by most guidelines.

On the other hand, Stakeholder Involvement (44,44% ± 19,89%.) and Applicability (4,87% ± 1,39%) were not effectively addressed by none of the appraised guidelines.

Appendix 2 details the individual scores each of the 23 items of the different domains graded by the evaluators, by averaging the scores from each of the 4 appraisers.

Strength of recommendation's correspondence

Standardized categories were made for equal comparison of the strength of recommendations across guidelines (*Figure 2*). These categories were adapted from the grading system used by the BMJ Clinical Evidence, using the labels: "beneficial", "likely to be beneficial", "trade-off between benefits and harms", "likely to be ineffective or harmful" and "unknown effectiveness" for each intervention (*Appendix 3*).

BMJ Clinical Evidence developed these categories of effectiveness from one of the Cochrane Collaboration's products.[50] Fitting interventions into these categories is not always straightforward and the categories represent a combination of several hierarchies: the size of benefit (or harm), the strength of evidence (randomized clinical trials or observational data), and the degree of certainty around the finding (represented by the confidence interval).[51,52]

The categories took into consideration that guidelines had different scoring systems such that any recommendation was put in an equivalent category than it had in the original guideline.

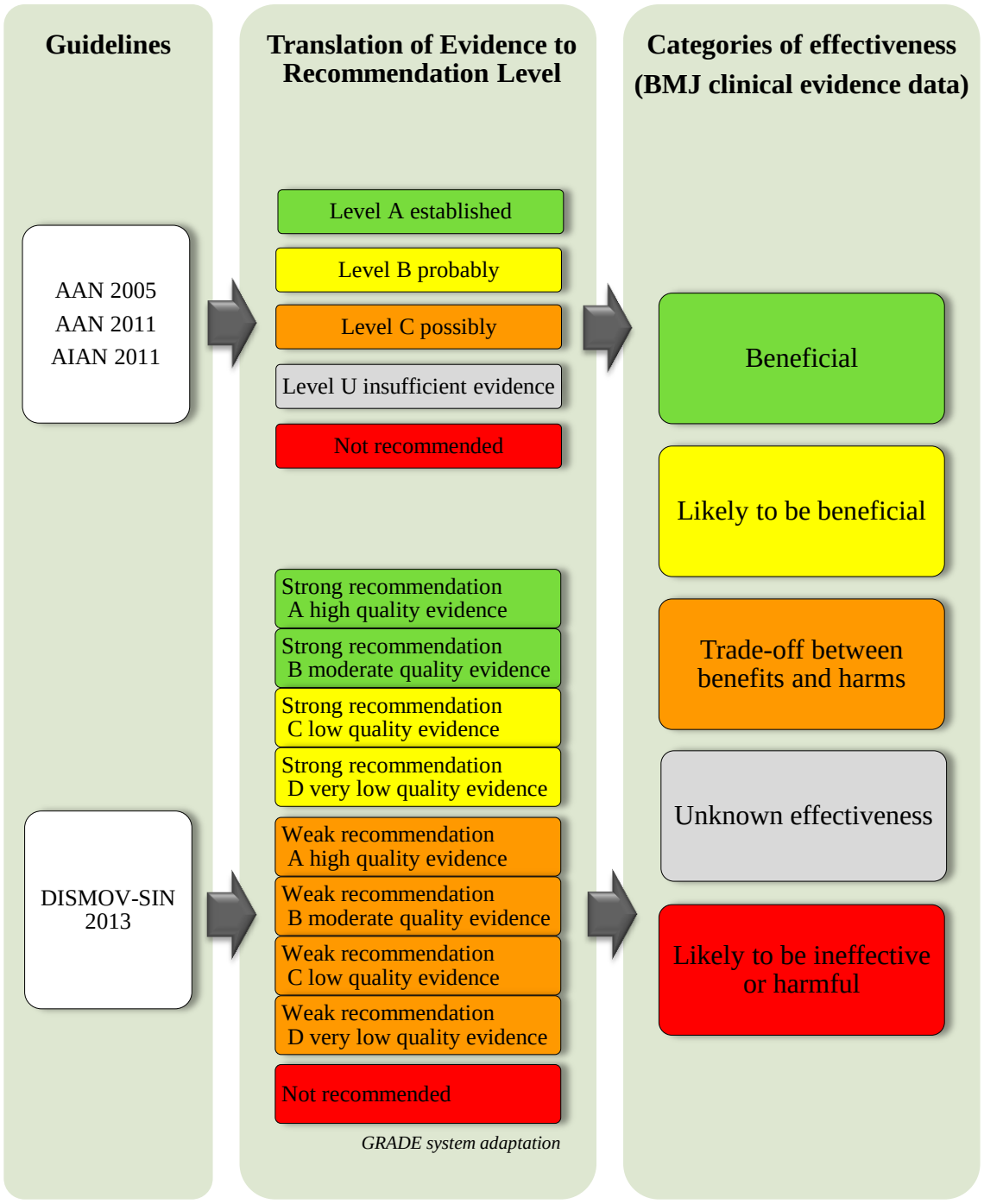

Figure 2. Standardised categories and correspondence for equal comparison of recommendations across guidelines

Guidelines Recommendations

Table 3 summarizes the recommendations concerning essential tremor treatment included in the guidelines. Four guidelines [42-45] had their strength of recommendations provided by the developers. One guideline [46] was excluded from data extraction because no grading system was given in the article. Three guidelines have ongoing translation processes[47-49]

The recommendations formulated by these guidelines were categorized considering the form of tremor targeted in each recommendation – limb tremor, head tremor, voice tremor – and further organized based on pharmacological and surgical treatments.

***Table 3*:** Selected guideline summary of recommendations

	Guideline Developer						
	AAN 2005[42]	**AAN update 2011[43]**	**AIAN 2011[44]**	**DISMOV-SIN 2013 [45]**	**DGN 2012 [47]**	**JSNT 2011[48]**	**CAN 2009 [49]**
Limb Tremor							
Pharmacologic treatment							
β-blockers							
Propranolol	Beneficial	Beneficial	Beneficial	Beneficial			
Propranolol LA	Beneficial	Beneficial	Beneficial	Beneficial			
Sotalol	Likely beneficial	Likely beneficial	Likely beneficial[2]	Likely beneficial[2]			
Atenolol	Likely beneficial	Likely beneficial	Likely beneficial[2]	Trade-off between benefits / harms[2]			
Nadolol	Trade-off between benefits / harms	Trade-off between benefits / harms	Likely beneficial[2]	Trade-off between benefits / harms[2]			
Metoprolol	Unknown effectiveness	Unknown effectiveness		Trade-off between benefits / harms[2]			
Pindolol	Likely ineffective or harmful	Likely ineffective or harmful		Likely ineffective or harmful			
Arotinolol				Likely beneficial[2]			
Timolol				Trade-off between benefits / harms[2]			
ICI 118.551				Trade-off between benefits / harms[2]			
LI32-468				Trade-off between benefits / harms[2]			
Bufetolol				Trade-off between benefits / harms[2]			
Oxprenolol				Trade-off between benefits / harms[2]			
Indenolol				Trade-off between benefits / harms[2]			
Anticonvulsants							
Primidone	Beneficial	Beneficial	Beneficial	Beneficial			
Topiramate	Likely beneficial	Likely beneficial	Likely beneficial[2]	Beneficial			
Gabapentin	Likely beneficial	Likely beneficial	Likely beneficial[2]	Likely beneficial[2]			
Gabapentin (adjunct therapy)	Unknown effectiveness	Unknown effectiveness					
Phenobarbital	Unknown effectiveness	Unknown effectiveness		Likely ineffective or harmful			
Acetazolamide	Likely ineffective or harmful	Likely ineffective or harmful					
Zonisamide		Unknown effectiveness	Trade-off between benefits / harms[2]	Likely beneficial[2]			
Levetiracetam		Likely ineffective or harmful		Likely ineffective or harmful			
Pregabalin		Unknown effectiveness	Likely beneficial[2]	Likely ineffective or harmful			
Progabide				Likely ineffective or harmful			
BarbiturateT2000				Likely ineffective or harmful			

Benzodiazepines				
Alprazolam	Trade-off between benefits / harms	Trade-off between benefits / harms	Trade-off between benefits / harms[2]	Likely beneficial[2]
Clonazepam	Trade-off between benefits / harms	Trade-off between benefits / harms	Trade-off between benefits / harms[2]	Likely ineffective or harmful
Lorazepam			Trade-off between benefits / harms[2]	
Diazepam			Trade-off between benefits / harms[2]	
Neuroleptics				
Clozapine	Trade-off between benefits / harms[2]	Unknown effectiveness	Trade-off between benefits / harms[2]	Trade-off between benefits / harms[2]
Olanzapine	Unknown effectiveness	Unknown effectiveness		Likely beneficial
Quetiapine	Unknown effectiveness	Unknown effectiveness		Likely ineffective or harmful
Antidepressants				
Mirtazapine	Likely ineffective or harmful	Likely ineffective or harmful		
Trazodone	Likely ineffective or harmful	Likely ineffective or harmful		
Calcium channel blocker				
Nimodipine	Trade-off between benefits / harms	Trade-off between benefits / harms	Likely beneficial[2]	
Nicardipine	Unknown effectiveness	Unknown effectiveness		
Nifedipine	Likely ineffective or harmful	Likely ineffective or harmful		
Verapamil	Likely ineffective or harmful	Likely ineffective or harmful		
Flunarizine		Likely ineffective or harmful		
Amantadine	Unknown effectiveness	Unknown effectiveness		Likely ineffective or harmful
Clonidine	Unknown effectiveness	Unknown effectiveness		
Glutethimide	Unknown effectiveness	Unknown effectiveness		
L-tryptophan/pyridoxine	Unknown effectiveness	Unknown effectiveness		
Theophylline	Unknown effectiveness	Unknown effectiveness		
Isoniazid	Likely ineffective or harmful	Likely ineffective or harmful		
Methazolamide	Likely ineffective or harmful	Likely ineffective or harmful		
3,4-diaminopyridine		Likely ineffective or harmful		
Botulinum toxin A	Trade-off between benefits / harms[2]	Trade-off between benefits / harms[2]		Likely beneficial[2]
Combination therapy				
Propranolol + Primidone	Likely beneficial[1]			Likely beneficial[1]
Surgical treatment				
Unilateral Thalamic DBS	Trade-off between benefits / harms[2]	Trade-off between benefits / harms[2]		Likely beneficial[3]
Bilateral Thalamic DBS			Trade-off between benefits / harms[3]	Likely ineffective or harmful
Subthalamic nucleus DBS				Trade-off between benefits / harms[3]
Unilateral Thalamotomy	Trade-off between benefits / harms[3]	Trade-off between benefits / harms[3]	Trade-off between benefits / harms[3]	Likely ineffective or harmful
Bilateral Thalamotomy	Likely ineffective or harmful	Likely ineffective or harmful	Likely ineffective or harmful	
Gamma knife surgery	Unknown effectiveness	Unknown effectiveness		

Head Tremor				
Pharmacologic treatment				
Propranolol	Likely beneficial	Likely beneficial		
Botulinum toxin A	Trade-off between benefits / harms	Trade-off between benefits / harms		Likely beneficial[2]
Surgical treatment				
Unilateral Thalamic DBS	Unknown effectiveness	Unknown effectiveness		
Bilateral Thalamic DBS			Unknown effectiveness	Likely ineffective or harmful
Unilateral Thalamotomy				
Gamma knife surgery				
Voice Tremor				
Pharmacologic treatment				
Botulinum toxin A	Trade-off between benefits / harms	Trade-off between benefits / harms		Trade-off between benefits / harms[2]
Surgical treatment				
Unilateral Thalamic DBS	Unknown effectiveness	Unknown effectiveness		
Bilateral Thalamic DBS			Unknown effectiveness	Likely ineffective or harmful
Unilateral Thalamotomy				
Gamma knife surgery				
Orthostatic Tremor				
Pharmacologic treatment				
Clonazepam			Likely beneficial[2]	
Behavioral Techniques and Physical Therapy				
Relaxation therapies			Likely beneficial[4]	
Reducing emotional stress			Likely beneficial[4]	
Using the less disabled hand			Likely beneficial[4]	
Using wrist weights			Likely beneficial[4]	
Minimizing exposure to tremorogenic foods and drugs			Likely beneficial[4]	

Standardized categories: Beneficial interventions are highlighted green; **Likely beneficial** interventions are highlighted yellow; **Trade-off between benefits/harms** interventions are highlighted orange; Interventions of **Unknown effectiveness** are highlighted in grey. **Likely ineffective or harmful** interventions are highlighted in red.

1*. when monotherapy does not sufficiently reduce tremor*

2*. as second-line treatment*

3*. refractory to medical therapies*

4*. in patients with less disabling tremor*

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***Appendix 1*:** Criteria applied to select eligible articles for appraisal

	Inclusion criteria	Rationale for the criteria	Exclusion criteria
1.	**Article identifying itself as "guidelines", "recommendations", "practice parameters", "practice guidelines", "standards of practice", "standard treatment", "algorithm", "consensus" or "expert opinion"**	Fulfill the purpose of this review	Articles that do not meet the terms mentioned in the inclusion criteria, or that concern specific forms of tremor other than the subject of this review
2.	**Title or abstract includes one or more of the following terms: "tremor", "essential tremor", "action tremor", "postural tremor", "kinetic tremor", "intention tremor", "familial tremor", "benign tremor", "movement disorders", "neurological diseases"**		
3.	**Guidelines that include treatment of Essential Tremor, either non pharmacological, medical or surgical.**	Only articles that focus on the subject of this review were included.	Guidelines that do not focus on treatment of Essential Tremor
4.	**All languages included**	Identify as many existing guidelines or recommendations as possible, including international, national or local ones that focus on the subject of this review.	
5.	**Produced at international, national or local levels by medical associations or governmental bodies**		
6.	**All available publications until Jan 2016 were included**		
7.	**Publication type: practice guidelines, consensus statement, expert opinion**	Practice guidelines may be developed by government agencies at any level, institutions, organizations such as professional societies or governing boards, or by the convening of expert panels [1], with the purpose of guiding decisions in clinical practice.	Publication type: exclusively systematic reviews of the evidence, research articles, clinical trials, case reviews or consensus statements without supporting evidence

[1] Source:http://www.nlm.nih.gov/mesh/pubtypes.html

***Appendix 2*:** Data from AGREE II evaluation with scores for each item

	Guideline Developer							
	AAN 2005	**AAN 2011**	**AIAN 2011**	**DISMOV-SIN 2013**	**SWEMODIS 2014**	**DGN 2012**	**JSNT 2011**	**CAN 2009**
Domain 1. Scope and Purpose								
1	5,00	5,00	2,00	7,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
2	6,00	6,00	3,00	6,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
3	5,00	4,00	2,33	6,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Domain 2. Stakeholder Involvement								
4	5,00	6,00	3,67	5,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
5	1,00	1,00	1,00	1,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
6	6,67	6,33	1,00	5,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Domain 3. Rigor of Development								
7	5,67	6,00	1,00	7,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
8	6,00	6,00	1,00	7,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
9	4,33	5,00	1,33	6,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
10	1,67	1,33	1,00	6,33	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
11	6,67	6,33	5,33	6,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
12	6,67	6,67	2,67	7,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
13	2,33	5,00	1,00	6,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
14	1,33	1,00	1,00	1,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Domain 4. Clarity of Presentation								
15	6,67	6,33	4,00	7,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
16	6,33	6,00	6,00	6,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
17	6,67	6,33	6,67	6,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Domain 5. Applicability								
18	1,00	1,00	1,00	1,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
19	1,67	2,33	2,33	2,33	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
20	1,00	1,00	1,00	1,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
21	1,00	1,00	1,00	1,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Domain 6. Editorial Independence								
22	4,00	6,00	1,00	3,33	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
23	1,00	6,33	5,33	5,67	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
Overall assessment								
	4,00	5,00	2,00	6,00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!

AAN: American Academy of Neurology; **AIAN**: Annals of Indian Academy of Neurology; **DISMOV-SIN:** Italian Movement Disorders Association; **DGN**: German Society of Neurology; **SWEMODIS:** Swedish Movement Disorders Society; **JSNT:** Japanese Society of Neurological Therapeutics; **CAN:** Chinese Association of Neurology.

***Appendix 3*:** Categories of effectiveness by the BMJ Clinical Evidence Data

Intervention	Icon	Description
Beneficial		For which effectiveness has been demonstrated by clear evidence from systematic reviews, RCTs, or the best alternative source of information and for which expectation of harms is small compared with the benefits.
Likely to be beneficial		For which effectiveness is less well established than for those listed under "beneficial".
Trade-off between benefits and harms		For which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities.
Unknown effectiveness		For which there are currently insufficient data or data of inadequate quality.
Likely to be ineffective or harmful		For which ineffectiveness or associated harm has been demonstrated by clear evidence.

http://clinicalevidence.bmj.com/x/set/static/cms/nuts-and-bolts.html

BMJ Group. Clinical Evidence Handbook. BMJ Evidence Centre, June 2011